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Rational of Current Practice of Prescribing Statin to Treat Dyslipidaemia as Primary Prevention of Coronary Heart Disease in Elderly People

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ABSTRACT

Background: The efficacy of statin therapy in preventing both primary and secondary coronary heart diseases in young and middle aged people is well known and well supported by numbers of landmark clinical trials. Literatures addressing reduction of cholesterol level in elderly (septogenarians & octogenarians) as primary prevention strategy for coronary heart diseases are scarce. The elderly population rarely suffer from primary heart attack and as such routine prescribing of statin to treat dyslipidaemia as primary prevention of coronary heart disease is controversial, particularly when there are reports that statin therapy in elderly population causes cancer, haemorrhagic stroke, dementia and so on. The present study was aimed at answering these questions in order to help formulating a separate guideline for statin therapy in elderly.

Methods: The present study reviewed literatures of recent and recent past origin. A systematic literature search of MEDLINE, EMBASE, CINAHL, Web of Science, CANCERLIT and the Cochrane Systematic Review Database have been used to identify randomized clinical trials of statin use with the main focus on primary or secondary end point of CHD, acute coronary syndrome (ACS), cardiac death, overall death, stroke and cancer diagnosis or cancer death. To be included in this review, (1) the entire study subjects or a sub-group were of age 55 years or more (2) had a mean (or median) duration of patient follow-up of at least 1 year, (3) enrolled a minimum of 100 patients, and (4) reported data on the incidence of either cancer diagnosis or cancer death in the elderly population.

Conclusions: The study concludes that statin therapy in elderly people may not provide additional benefit in the prevention of primary cardiovascular diseases or death due to primary cardiovascular events. Though most of the studies ruled out excess risk of cancer or other noncardiovascular events, their probability cannot be entirely ignored. However, there is report that addition of statin to the existing drug schedule of elderly subjects does not cause drug interaction. Large-scale, randomized trial on truly representative population with long term follow up will provide authentic data to answer the question whether statin therapy in elderly people with dyslipidaemia can prevent primary heart diseases.

Key words: Statin, primary prevention, coronary heart disease, dyslipidemia, elderly people.

Introduction

Elderly group is now a large and growing segment of population that requires a special care when treatment options are considered. Despite these growing numbers little evidence is available to guide treatment decision for coronary artery disease in geriatric population. Though treatment effectiveness is available, treatment failure, compliance, cost effectiveness, adverse reactions etc. are not adequately addressed. There is growing need to consider these issues with utmost care whether we are offering true benefit to this subgroup of population. Very few studies have been focused towards this group on primary prevention of cardiovascular diseases (CVDs), where major questions and controversies still prevailing. Hence a separate practice guideline is a pressing need to manage the elderly group having elevated level of cholesterol without any evidence of coronary heart disease.

Objectives

The contemplated review therefore, intended to address the following objectives.

1. To evaluate whether statin therapy is at all necessary in elderly subjects with dyslipidaemia as primary prevention of coronary heart diseases.
2. To weigh the risks and benefits of statin therapy in elderly subjects having dyslipidaemia.
3. To put forward some recommendations to help formulating a guideline for prescribing of statin therapy, if it is deemed essential, in elderly subjects with dyslipidaemia.

Methodology

As the main purpose of our study is literature review and to come to a conclusion 'whether the current practice of prescribing statin to treat dyslipidaemia as primary prevention

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Review Article

of coronary heart disease at all necessary in all elderly people' from the reviewed literatures, it is essential to describe what methodology was adopted to review the literatures and how conclusions were drawn. The literatures of both recent and recent past origin were considered of immense value and were reviewed in-depth and were evaluated in terms of:

Design: Whether the study was an experimental, longitudinal or observational one? Double-blind randomised controlled trial was ranked highest followed by, cohort, case-control and cross-sectional studies.

Type of study population, sample size and sampling procedure: Whether the study population was rightly selected for the design contemplated? Whether the size of the sample and sampling procedure was statistically valid to measure what it intended to measure?

Exposure and outcome (disease) definitions: Whether the exposure and outcome (disease) was defined/operationalised before the start of study? Whether the diagnosis was validated by the latest available diagnostic techniques?

Power of the study: What was the power of the study? If the power of the study was below 80% it was considered as a weaker study to generalize the findings of the study to the reference population.

Test statistics used to analyse the data: Whether appropriate test statistics were employed to analyse the data depending upon the type of data and nature of distribution.

Causal association: Based on the above criteria if an association was observed between the exposure/factor and outcome, causal association was determined by modified Hill's Criteria. The criteria that were used to determine the relationship between the events was coincidental, causal or had interaction of another nature were initially defined in the 1960s by Hill. These criteria have been revised several times and most experts now agree on the use of following criteria to assess causality.

Strength of association: In general, the stronger the association, the lower the likelihood that the results are attributable to chance. Where there is strong association and the suspect factor frequently results in disease, small studies usually can reveal a causal association.

Consistency of association: If similar results are found in different studies conducted in different populations, it provides strong evidence for or against causal inference.

Specificity of association: Finding a single adverse event associated with the factor in question provides more suggestive evidence of a causal association than if multiple unrelated events are found.

Temporal association: A causal association is more strongly suggested if the adverse events are clustered in time after the exposure than if the events are distributed over a longer and more varied time interval.

Biologic gradient: The presence of a dose-response effect of drug or toxin provides increased evidence of causal association.

Biological plausibility: If the adverse event is consistent with known effects of the factor (exposure) in question, the evidence of causal association is strengthened.

Coherence: The evidence should fit together into a reasonable explanation for the observed association between the exposure and the event of interest.

Experimental evidence: Intervention studies that test a hypothesis can provide evidence for or against causal inference.

In general, the evidence related to benefit or harm of specific interventions is derived from multiple sources. These include: epidemiological observational studies which identify associations; clinical research and large-scale randomised clinical trials to establish efficacy, net benefit and cost-effectiveness; randomised clinical trials to establish safety and outcomes research and long-term surveillance data to allow an estimate of outcomes and effectiveness in clinical practice.

Study Selection

We conducted a systematic literature search of MEDLINE from 1966 through July 2005, EMBASE from 1990 through July 2005, CINAHL from 1982 through July 2005, Web of Science from 1994 through July 2005, CANCERLIT from 1975 through July 2005, and the Cochrane Systematic Review Database to identify randomized clinical trials of statin use with a primary or secondary end point of cancer diagnosis or cancer death. References were also retrieved from lists of articles and previous reviews and meta-analyses on lipid-lowering treatment. The search was restricted to trials in human beings that were published in or translated into English. A search strategy using the Medical Subject Heading and text key words statin, primary prevention of CHD, elderly were used. In addition, a manual review of references from primary or review articles was performed to identify any additional relevant studies. We also conducted a "cited-reference search" in Web of Science for all eligible papers, reviewed the reference lists of all included studies and review articles.

Eligibility Criteria

To be included in this review, (1) the entire study subjects or a sub-group were of age 55 years or more (2) had a mean (or median) duration of patient follow-up of at least

1 year, (3) enrolled a minimum of 100 patients, and (4) reported data on the incidence of either cancer diagnosis or cancer death in the elderly population.

Data abstraction

The following information was sought from each article: author identification, year of publication, geographic location of the study, study design (prospective or retrospective, randomized or observational, presence and type of control, blinded or open-label), study population, sample size, duration of patient follow-up, statin used, type of cancer diagnoses included (breast, prostate, colon, respiratory, gastrointestinal, or melanoma), cancer death (when reported), and method of data collection within trials for cancer end points. In cases of more than one published report on the same population or group of patients, the most recent article was selected for analysis.

Literatures Reviewed

Observational studies in different populations indicate a continuous positive relationship between coronary heart disease risk and blood LDL cholesterol concentration that extends well below the range currently seen in Western populations, without any definite "threshold" below which a lower concentration is not associated with lower risk.[1,2,3]

Recently, large randomised trials have shown that lowering LDL cholesterol with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) reduces coronary mortality and morbidity in some types of high-risk patient.[4,5,6,7] Typically in those trials, an average reduction in LDL cholesterol of about 1 mmol/L maintained for about 5 years caused a reduction in non-fatal myocardial infarction and coronary death of about one-quarter. In United Kingdom population as well, it is therefore expected that reducing LDL cholesterol may reduce the development of vascular disease, whatever the initial cholesterol concentrations be.

With such intention Heart Protection Study Collaborative Group randomly allocated 20,536 UK adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabetes to receive 40 mg simvastatin daily (average compliance: 85%) or matching placebo (average non-study statin use: 17%). Analyses were of the first occurrence of particular events which were compared between all simvastatin-allocated versus all placebo-allocated participants. Primary outcomes were mortality (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity.8 The findings derived showed that all-cause mortality was significantly reduced (12.9% deaths among 10,269 allocated simvastatin versus 14.7% among 10,267 allocated placebo; p = 0.0003). There were highly significant reductions of about one-quarter in the first event rate for nonfatal myocardial infarction or coronary death (8.7% vs. 11.8%, p < 0.0001), for non-fatal or fatal stroke (4.3% vs. 5.7%, p < 0.0001), and for coronary or noncoronary revascularisation (9.1% vs. 11.7%;p < 0.0001). For the first occurrence of any of these major vascular events, there was a definite 24% (SE 3; 95% CI 19-28) reduction in the event rate.[8]

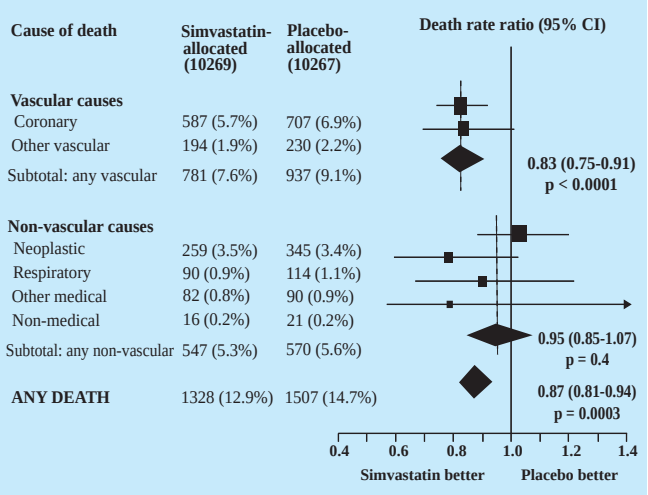

Fig1. *Effects of simvastatin allocation on cause-specific mortality Rate ratios (RRs) are plotted (black squares with area proportional to the amount of statistical information in each subdivision) comparing outcome among participants allocated simvastatin to that among those allocated placebo, along with their 95% CIs (horizontal lines; ending with arrow head when CI extends beyond scale). For particular subtotals and totals, the result and its 95% CI are represented by a diamond, with the RR (95% CI) and its statistical significance given alongside. Squares or diamonds to the left of the solid vertical line indicate benefit with simvastatin, but this is conventionally significant (p<0.05) only if the horizontal line or diamond does not overlap the solid vertical line. A broken vertical line indicates the overall RR for a particular subtotal or total (Adapted from HPS Collaborative Group, 2002).*

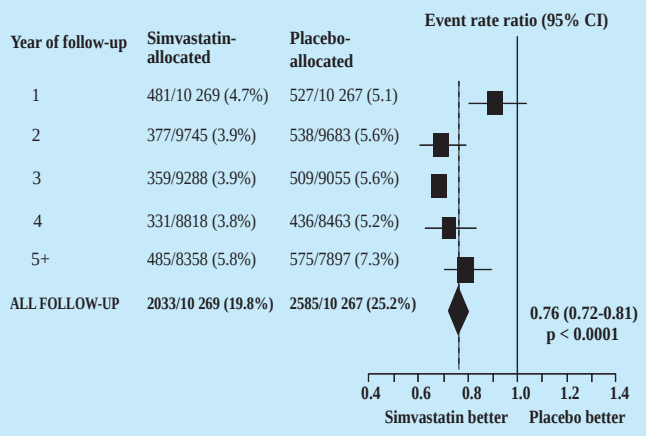

Fig2. Effects of simvastatin allocation on first major vascular event during follow-up Symbols and conventions as in figure 1. Analyses are of numbers of participants having a first event during each year of follow-up and of those still at risk of a first event at the start of each year (Adapted from HPS Collaborative Group, 2002).

During the first year the reduction in major vascular events was not significant, but subsequently it was highly significant during each separate year. The proportional reduction in the event rate was similar (and significant) in each subcategory of participants studied, including those without diagnosed coronary disease who had cerebrovascular disease, or peripheral artery disease, or diabetes; men and women separately; those aged either under or over 70 years at entry; and-most notably-even those who presented with LDL cholesterol below 3·0 mmol/L (116 mg/dL), or total cholesterol below 5·0 mmol/L (193 mg/dL). The simvastatin provides additional benefits to those of other cardioprotective treatments. The annual excess risk of myopathy with this regimen was negligible (0·01%). There were no significant adverse effects on cancer incidence or on hospitalisation for any other non-vascular cause.

Lowering cholesterol with 40 mg simvastatin daily produces substantial reductions in the rates of major vascular events among a wide range of high-risk individuals irrespective of their initial cholesterol concentrations, and these benefits are additional to those of other treatments, such as, aspirin, ß-blockers, angiotensin-converting-enzyme inhibitors, and other antihypertensive therapy[9,10,11] that have also been shown to be beneficial for such people. During the study, an average of about one-sixth of the participants allocated 40 mg simvastatin daily stopped taking statin therapy, and about one-sixth of those allocated placebo started to take a statin.

Hence, actual use of 40 mg simvastatin daily would lower LDL cholesterol by about 1·5 mmol/L in this population and would probably reduce the rates of heart attacks, strokes, and revascularisations by about one-third. Consequently, among the types of high-risk individuals studied (with 5-year placebo-group event rates of about 20-30%), treatment for 5 years should prevent about 70-100 people per 1000 from suffering at least one of these major vascular events, largely irrespective of age, sex, or presenting cholesterol concentrations. It seems likely, therefore, that such treatment will be considered worthwhile for many types of high-risk patients who are not currently being treated, particularly since it has been shown to be so well tolerated and safe.

A randomised double-blind study conducted on 6595 men, 45 to 64 years of age with hypercholesterolemia and no history of myocardial infarction to determine whether the administration of pravastatin to men reduced the combined incidence of non-fatal myocardial infarction and death from coronary heart disease. The mean plasma cholesterol level of the participants was 272 ± 23 mg per deciliter. The participants either received pravastatin (40 mg each evening) or placebo (average follow-up period was 4.9 years). Medical records, ECG recordings, and the national death registry were used to determine the clinical end points.[4] The result showed that pravastatin lowered plasma cholesterol levels by 20% and low-density lipoprotein cholesterol levels by 26%, whereas there was no change with placebo. The study also observed that treatment with pravastatin significantly reduced the incidence of myocardial infarction and death from cardiovascular causes without adversely affecting the risk of death from noncardiovascular causes in men with moderate hypercholesterolemia and no history of myocardial infarction.[4] But this study does not stand to reason that paravastatin does not increase the risk of death from noncardiovascular causes, firstly because the study population was 40 - 64 years old, the age at which the risk of death from cancer is less, secondly the median follow up period was 4.9 years which did not have the scope of including noncardiovascular adverse event data beyond 5 years.

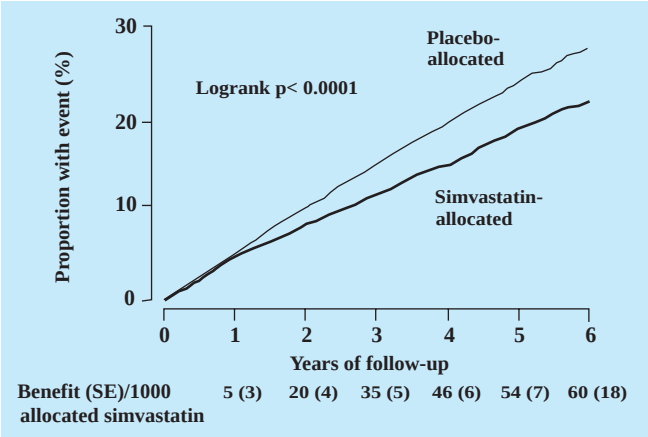

Fig 3. *Life-table plot of effects of simvastatin allocation on percentages having major vascular events (Adapted from HPS Collaborative Group, 2002).*

To determine the effect of statins on all-cause mortality and on major cardiovascular events, including stroke, Roberts and colleagues[12] performed a meta-analysis of statin trials that included older adult participants. Mortality, cardiovascular events, and adverse event outcomes were extracted from published randomized, placebo-controlled clinical trials of persons aged 60 years and older. Data on 51,351 patients were evaluated. Statins reduced all-cause mortality by 15% (95% confidence interval, 7-22%), coronary heart disease (CHD) death by 23% (15-29%), fatal or nonfatal myocardial infarction (MI) by 26% (22-30%), and fatal or nonfatal stroke by 24% (10-35%). The relative risk of cancer comparing statins to placebo was 1.06 (0.95-1.18). The study concludesthat statin therapy significantly reduced all-

cause and CHD mortality, as well as risk of stroke and MI. Statin therapy should be offered to older patients at high risk of atherosclerotic disease events.

As recent concerns have been expressed about the benefits of lipid-lowering specifically in elderly people,[13] Timo and associates[14] followed up a group of home-dwelling elderly patients (n = 400, average age 80 years, range 75 to 90 years, 65% women) for 6 years. At baseline (in the year 2000), the medical history, functional status, and current drug use were carefully examined, and a wide array of clinical and laboratory variables, including serum lipids, were measured. From baseline data they calculated the Dutch risk score, which included age, sex, body mass index, pulse rate, systolic blood pressure, smoking, hypertension, diabetes, and history of myocardial infarction. Comorbidity was measured with the Charlson comorbidity index.[15]

Of the patients, 80.8% (n = 323), 36.5% (n = 146), 13.8% (n = 55) and 20.8% (n = 83) had a history of coronary heart disease, cerebrovascular disorders, or peripheral artery disease amd use of statin respectively. In addition, a substantial proportion of patients had a history of malignant, thyroid, pulmonary, or gastrointestinal diseases. The mean Charlson index was 2.5 ± 1.5. Median Mini-Mental State Examination (MMSE) score was 27, and 60 individuals had a score below 24 points. During the 6-year follow-up, 129 (32.3%) individuals died. Unadjusted survival curves according to statin treatment at baseline are shown in figure 4. Statin use was associated with a 46% reduced total mortality risk (RR = 0.54, 95% 0.32-0.91) after adjustment for baseline risk score, cognitive function, Charlson index, and HRQoL.

The study concludes that in age 75 and older population with comorbidities, statin treatment was associated with a clearly reduced 6-year mortality risk. In general, the relationship between cholesterol and mortality and morbidity is not straightforward in old age, as is also reflected in studies.16,17 The relationship is complicated by the fact that an underlying pathologic condition may both lower cholesterol level and increase mortality risk. Therefore higher cholesterol may paradoxically reflect better prognosis in epidemiological studies. Their result is in accordance with the results from randomized trials of therapeutically lowered cholesterol.[11] It also concurs with earlier observational data of cardiovascular disease reduction in older patients treated with statins,[18] and suggests that benefits may be even higher in real life than in clinical trials. This study is in agreement with the findings of meta-analysis reported by Roberts and colleagues that older patients at cardiovascular risk should not have statin therapy withheld.

A multicenter (513 primary community-based North American clinical centers), randomized, nonblinded trial conducted from 1994 through March 2002 in a subset of participants from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)[19] to determine whether pravastatin compared with usual care reduces all cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor (ALLHAT CRG, 2002).[20] Ambulatory persons (n=10355), aged 55 years or older, with low-density lipoprotein cholesterol (LDL-C) of 120 to 189 mg/dL (100 to 129 mg/dL if known CHD) and triglycerides lower than 350 mg/dL, were randomized to pravastatin (n = 5170) or to usual care (n = 5185). Baseline mean total cholesterol was 224 mg/dL; LDL-C, 146 mg/dL; high-density lipoprotein cholesterol, 48 mg/dL; and triglycerides, 152 mg/dL. Mean age was 66 years, 49% were women, 38% black and 23% Hispanic, 14% had a history of CHD, and 35% type 2 diabetes.

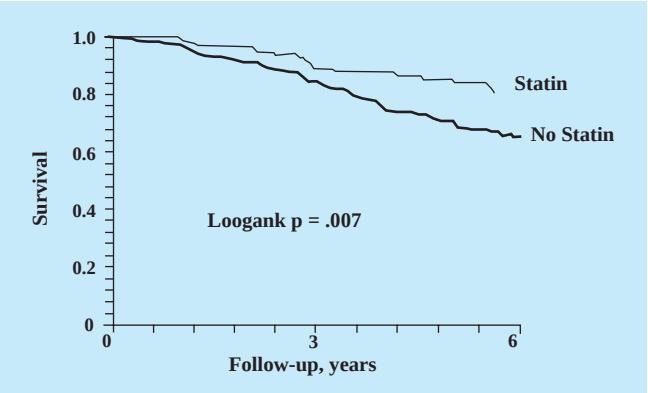

Fig 4. *Six-year survival according to the baseline statin use in the DEBATE [Drugs and Evidence Based Medicine in the Elderly] study population (n = 400)*

The pravastatin group received 40 mg pravastatin daily, the usual care group received usual treatment without any lipid lowering drugs. The primary outcome was all-cause mortality, with follow-up for up to 8 years. Secondary outcomes included nonfatal myocardial infarction or fatal CHD (CHD events) combined, cause-specific mortality, and cancer. Mean follow-up was 4.8 years. During the trial, 32% of usual care participants with and 29% without CHD started taking lipid-lowering drugs. At year 4, total cholesterol levels were reduced by 17% with pravastatin vs. 8% with usual care; among the random sample who had LDL-C levels assessed, levels were reduced by 28% with pravastatin vs. 11% with usual care. All-cause mortality was similar for the 2 groups (RR = 0.99; 95% CI = 0.89-1.11; P = 0.88), with 6-year mortality rates of 14.9% for pravastatin and 15.3% with usual care. CHD event rates were not significantly

different between the groups (RR, 0.91; 95% CI, 0.79-1.04; P =.16), with 6-year CHD event rates of 9.3% for pravastatin and 10.4% for usual care.

Pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants with well-controlled hypertension and moderately elevated LDL-C. The results may be due to the modest differential in total cholesterol (9.6%) and LDL-C (16.7%) between pravastatin and usual care compared with prior statin trials supporting cardiovascular disease prevention.[19]

ALLHAT provided a diverse population base for ALLHAT-LLT. This study, comparing pravastatin with usual care, assessed the value of cholesterol lowering in a population underrepresented in prior cholesterol trials-individuals with well-controlled hypertension, almost half women, 38% black, 35% with a history of diabetes, 55% at least 65 years of age, and 25% with LDL-C lower than 130 mg/dL (3.4 mmol/L). Adherence to pravastatin in ALLHAT-LLT, 80% at 4 years of follow-up, was comparable to adherence in other large statin trials[7,8,19,20] and decreased levels of total cholesterol by 17% and LDL-C by 28% from baseline. However, unlike other statin trials, the study found no significant reductions in total mortality, CHD or stroke with pravastatin vs. usual care. There are several possible explanations for the findings of ALLHAT-LLT, including the smaller than expected differential in total cholesterol between the 2 groups; the trial's unique participant population and the study's non-blinded design.

Cholesterol Differential Between Pravastatin and Usual Care

The usual care group had reductions of 8% in total cholesterol and 11% in LDL-C at 4 years, in contrast to other placebo-controlled statin trials, which observed little or no cholesterol reduction in the placebo groups. The resulting 9.6% total cholesterol differential was less than half the average for several other long-term statin trials with at least 1000

participants.[7,8,20] However, because of the modest cholesterol differential between pravastatin and usual care, ALLHAT-LLT lacked the power to discriminate between the expected reductions in mortality and CHD events and the null hypothesis. The reduction in study power was not due to low mortality rates; the number of deaths in the ALLHAT-LLT usual care group (641) differed only slightly from the estimate (625) used in the revised power calculation for a sample size of 10000. Moreover, the numbers of participants and deaths in ALLHAT-LLT were larger than in any other statin trial except the Heart Protection Study (2002).[8] The lack of study power likely was due to a failure to achieve a total cholesterol differential sufficient to yield the anticipated 20% reduction in mortality.

Finally, ALLHAT-LLT did not test the widely advanced hypothesis that statin treatment reduces CHD risk and mortality by mechanisms independent of cholesterol lowering (e.g., anti-inflammatory effects).[21] Furthermore, the observed differences in both CHD events and all cause mortality in ALLHAT-LLT were consistent with those predicted for a 10% total cholesterol differential in a model based on trials using a wide array of cholesterol-lowering interventions.

Unique Participant Population

ALLHAT-LLT included larger proportions of older participants, women, blacks, and Hispanics than any other statin trial completed. However, subgroup analyses of ALLHAT-LLT, like those of prior statin trials[6,8] do not show age- or sex-related differences in RRs for CHD event rates. The RR for pravastatin vs. usual care was significantly lower in blacks than non-blacks for CHD events but was higher for strokes, with no overall difference for combined cardiovascular events (data not shown). While the 14% of LLT participants with overt CHD at entry had higher event rates than those with comparable LDL-C levels (130 mg/dL) but without CHD, the pravastatin/usual care RRs for mortality and CHD were similar in both groups. These RRs were also unaffected by LDL-C level at baseline. By contrast, HPS Collaborative Group[8] reported similar estimates of benefits with simvastatin at all levels of LDL-C, while a pooled analysis of 3 large pravastatin trials[6] suggested benefit only in participants with LDL-C levels higher than 125 mg/dL (3.2 mmol/L).

However, ALLHAT-LLT was a nonblinded trial, designed and carried out during the period in which a series of landmark trials[7,8,20] and guidelines (NCEP Adult Treatment Panel II, 1993) stimulated the prescription of statins and progressively broadened the indications for their use in individuals targeted by ALLHAT-LLT. This may have contributed to the use of open label statins in the usual care group. Because the study was not blinded, there may also have been greater use of non-pharmacologic cholesterol-lowering interventions in usual care than in pravastatin, although changes in participants' diets, exercise habits, and weight were not examined in ALLHAT.

ALLHAT-LLT demonstrated no significant difference between pravastatin and usual care groups in all-cause mortality or combined fatal and nonfatal CHD. After including ALLHAT-LLT, the overall findings from the 9 large long-term statin trials (including ALLHAT-LLT) leave little doubt regarding the broad efficacy and safety

of this treatment in the prevention and treatment of atherosclerotic cardiovascular disease. In the absence of evidence for increases in any category of noncardiovascular mortality, the ALLHAT-LLT results should be interpreted as consistent with current recommendations for cholesterol control in the prevention and treatment of cardiovascular disease. These results emphasize the need for obtaining an adequate reduction in LDL-C in clinical practice when lipid-lowering therapy is implemented.

Patients with systolic heart failure have generally been excluded from statin trials for acute coronary events are uncommon in this population, and with the believe that statins would be risky in these patients. Kjekshus and his associates[22] put different opinions through his study. They included a total of 5011 patients at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure and randomly assigned them to receive 10 mg of rosuvastatin or placebo per day. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations.

The results obtained showed that patients in the rosuvastatin group had decreased levels of low-density lipoprotein cholesterol (difference between groups, 45.0%; P<0.001) and of high-sensitivity C-reactive protein (difference between groups, 37.1%; P<0.001). During a median follow-up of 32.8 months, the primary outcome occurred in 692 patients in the rosuvastatin group and 732 in the placebo group (hazard ratio, 0.92; 95% CI = 0.83 to 1.02; P = 0.12) and 728 patients and 759 patients, respectively, died (hazard ratio, 0.95; 95% CI = 0.86 to 1.05;

P = 0.31). There were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes. In a prespecified secondary analysis, there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group (2193) than in the placebo group (2564) (P < 0.001). No excessive episodes of muscle-related or other adverse events occurred in the rosuvastatin group. The conclusion drawn through these findings was that Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations. The drug did not cause safety problems.

Despite having favorable effects on lipids (a reduction in levels of LDL cholesterol and triglycerides and an increase in the level of HDL cholesterol) and on high-sensitivity C-reactive protein, a daily dose of 10 mg of rosuvastatin did not reduce the primary composite cardiovascular outcome or death from any cause when the drug was added to extensive background pharmacologic therapy in this previously unstudied population of older patients with moderate to severe ischemic systolic heart failure. Rosuvastatin reduced the number of hospitalizations for cardiovascular causes (154 fewer admissions per 1000 patients treated for a median follow-up of 2.7 years) and, as a result, reduced the total number of hospital admissions for any cause. Although in elderly patients who had renal impairment and muscle fatigue and who were at risk for hepatic congestion, rosuvastatin was not found to be associated with an excessive number of adverse events, a conclusion supported by the consistent finding of fewer primary events in the rosuvastatin group than in the placebo group in most high-risk subgroups. Nonfatal myocardial infarction and stroke were relatively uncommon in this population, and death from cardiovascular causes accounted for the majority of primary events.

On the basis of previous autopsy studies showing that approximately half of sudden deaths in patients with heart failure were due to plaque rupture and coronary occlusion,[23,24] the authors hypothesized that rosuvastatin therapy might also reduce the risk of sudden death in patients with ischemic heart failure. But why it did not is uncertain. However, several reasons were thought to play the role. The patients in their trial were also treated extensively with other drugs known to reduce the risk of sudden death, including angiotensin-converting-enzyme inhibitors, beta-blockers, and aldosterone antagonists. An alternative explanation for the lack of treatment benefit could be that rosuvastatin caused harm in a subgroup of patients, which offset a larger benefit in the remainder. This seems unlikely, since no such effect was identified in any of the subgroups of patients with prespecified risks and because there were fewer hospitalizations in the rosuvastatin group. Another possibility is that the patients were not followed long enough to see a beneficial effect of treatment.

The drug, rosuvastatin reduced the total number of hospitalizations for heart failure, perhaps because it prevented the development of acute coronary disease that would have contributed to such episodes. An alternative explanation is that rosuvastatin reduced myocardial ischemia by improving endothelial or microvascular function or by a direct or indirect effect on cardiomyocytes, through the suggested pleiotropic effects of these drugs.[22,25-27] Such data on hospitalizations and changes in the NYHA class and scores on the McMaster Overall Treatment Evaluation questionnaire refute previous speculation that statins might lead to a worsening

of heart failure. In addition, there was no significant excess in the number of muscle-related symptoms or elevations in creatine kinase levels in patients receiving rosuvastatin than in those receiving placebo. These findings suggest that the hypothetical detrimental effects of statins on the function of skeletal and cardiac muscle (and other physiological processes) do not result in important clinical consequences, nor was there any suggestion of the hypothetical risk of further reduction in LDL cholesterol in patients with already low levels.[22,25-29] There were also no more episodes of a significant elevation in liver aminotransferase levels, a worsening of renal function, or infections in the rosuvastatin group than in the placebo group. There were fewer treatment discontinuations and fewer deaths from noncardiovascular causes in the rosuvastatin group than in the placebo group.

However, the trial had some limitations. It studied older patients with moderate-to-severe heart failure who were in NYHA class III or IV (or who had an ejection fraction of 35% in NYHA class II) and whose physicians had not recommended that they should receive a statin. Since these patients may have had atherosclerotic or myocardial disease that was too advanced to modify, rosuvastatin might have had a different effect in patients with milder heart failure. The study did not investigate two other important groups of patients with heart failure: those with nonischemic heart failure and those with a preserved ejection fraction. Such patients have been enrolled in the study of Tavazzi *et al*[30] comparing rosuvastatin with placebo and n-3 polyunsaturated fatty acids with placebo in 6975 patients, with 4574 assigned to participate in the rosuvastatin portion of the study. The two primary outcome measures are the time to death and the time to either death or hospitalization for cardiovascular causes. Until the data of this study are published, it can be stated that daily treatment with 10 mg of rosuvastatin did not reduce the composite outcome of death from cardiovascular causes or nonfatal myocardial infarction or stroke in vulnerable, elderly patients with ischemic, systolic heart failure who had already received extensive treatment with drugs for cardiovascular disease. However, rosuvastatin reduced the number of hospitalizations for cardiovascular causes, in addition to effectively reducing levels of LDL cholesterol and high-sensitivity C-reactive protein.

The recently published results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial31 showed that After almost 5 years of follow-up, high-dose statin therapy (80 mg daily) could significantly reduce the risk of stroke in individuals with a recent stroke but no evidence of coronary heart disease (CHD). Its use resulted in a 16% reduction in the risk of stroke compared with patients on placebo. Of note, in these patients without any known CHD, the statin treatment was also accompanied by significant decreases in relative risk for cardiovascular events. The risk of major coronary events (cardiac death, nonfatal myocardial infarction was significantly reduced by 35% in the atorvastatin group. Significant reductions were also seen in the risk of major vascular events (major coronary event or stroke) or any CHD (acute coronary event, coronary revascularization, or angina/ischemia); in addition, revascularization was significantly reduced in the atorvastatin group (Table 1).

There was no statistically significant difference in all-cause mortality or cardiovascular mortality between the 2 study groups, although there was a trend toward a decrease in cardiovascular mortality with atorvastatin.

Although statins reduce coronary and cerebrovascular morbidity and mortality in middle-aged individuals, their efficacy and safety in elderly people is not fully established. In an attempt to test the benefits of pravastatin treatment in an elderly cohort of men and women with, or at high risk of developing, cardiovascular disease and stroke, Sheperd and their colleagues[5] carried out a randomised controlled trial in which 5804 participants (2804 men and women 3000) aged 70-82 years with a history of, or risk factors for, vascular disease were included. The participants were randomly assigned to receive either pravastatin 40 mg daily (n=2891) or placebo (n=2913). Baseline cholesterol concentrations ranged from 4·0 mmol/L to 9·0 mmol/L. Follow-up was 3·2 years on average and primary endpoint of treatment was a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke. Analysis was done on the basis of intention-to-treat.

Table 1. Cardiovascular Events between Atrovastatin and Placebo Groups

Cardiovascular Events	Atorvastatin No. (%)	Placebo No. (%)	HR	95% CI	P
Major coronary event	81 (3.4)	120 (5.1)	0.65	0.49-0.87	0.003
Major CV event	334 (14.1)	407 (17.2)	0.80	0.69-0.92	0.002
Any CHD	123 (5.2)	204 (8.6)	0.58	0.46-0.73	< 0.001
Any revascularization	94 (4.0)	163 (6.9)	0.55	0.43-0.72	< 0.001
Any CV event	530 (22.4)	687 (29.0)	0.74	0.66-0.83	< 0.001

CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio

The findings derived demonstrated that pravastatin lowered LDL cholesterol concentrations by 34% and reduced the incidence of the primary endpoint to 408 events compared with 473 on placebo (hazard ratio 0·85, 95% Cl = 0·74-0·97, p = 0·014). Coronary heart disease death and non-fatal myocardial infarction risk was also

reduced (hazard ratio = 0·81, 0·69-0·94, p = 0·006). Stroke risk was unaffected (p = 0·8), but the hazard ratio for transient ischaemic attack was 0·75 (0·55-1·00, p = 0·051). New cancer diagnoses were more frequent on pravastatin than on placebo (hazard ratio = 1·25, 1·04-1·51, p = 0·020). However, incorporation of this finding in a meta-analysis of all pravastatin and all statin trials showed no overall increase in risk. Mortality from coronary disease fell by 24% (p = 0.043) in the pravastatin group. Pravastatin had no significant effect on cognitive function or disability. As pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals, PROSPER study[32] advocated the same treatment strategy for elderly individuals as is currently used in middle aged people.

Over the period of 3 years, pravastatin produced a 15% relative reduction (2·1% absolute reduction) in the risk of the primary endpoint of treatment (a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke). The individuals on pravastatin had less coronary events than those on placebo, but rates of stroke remained the same. However, an apparent reduction in transient ischaemic attacks suggests that the treatment did have an effect on the cerebrovascular circulation. Pravastatin was well-tolerated in this patient population, who were taking a high number of concomitant medications, and there was no indication of adverse effects on liver function or muscle enzymes.

Results of previous long-term trials[6,7,8] have proven the benefits of cholesterol lowering treatment with statins. In these trials, about 50,000 individuals were randomly assigned to drug or placebo, and all had follow-up of around 5 years. Long-term trials of pravastatin accounted for about 20,000 of these individuals. Findings of the studies consistently showed benefit with a lack of associated concerns about safety. Results of PROSPER need to be interpreted in view of these earlier trials. The PROSPER Study differs from previous studies in several ways; by design, included men and women with a higher mean age than had been previously examined, combined both primary and secondary vascular disease prevention, and had a shorter follow-up.

Because of discrimination between the cardiovascular and cerebrovascular components of treatment benefit, the overall reduction in risk seen in the composite primary endpoint was less than predicted. This finding was not due to an inability to lower LDL cholesterol, since the 34% fall was greater than that seen in previous long-term trials of 40 mg per day pravastatin. The lack of effect on stroke might be the consequence of a lack of statistical power, or might follow from the short duration of the trial. Recent publications[33,34] suggest that stroke benefit from statins does not begin to appear until after 3 years, whereas coronary risk reduction is an early event.[8] Vascular factors contribute to cognitive impairment and dementia in old age.[35,36] This fact not only holds for large cortical infarcts and non-cortical micro-infarcts, but also for white-matter lesions, thought to be of vascular origin. The study tested the notion that treatment with statins might slow this decline.[37] The outcomes did not provide evidence for such benefit over the 3 years of the study. Lipophilic statins that efficiently cross the blood-brain barrier might work better than water soluble pravastatin. Five-year treatment with a high dose of the lipophilic simvastatin, however, did not prevent cognitive impairment.[8] Taken together, these experiments cast doubt on the suggestions from cross-sectional observations that statins might reduce risk of dementia by up to 70%.[38,39]

The potential for increased risk of cancer with the lowering of cholesterol was widely debated in the pre-statin era. Controversy arose from the finding of an inverse association between plasma cholesterol and cancer rates, especially in older persons, and from the results of early trials. More recent experience with statins in long-term trials allayed concerns that there was a cause and effect relation, and formal meta-analyses indicate no effect of these drugs on cancer incidence.[40,41] Furthermore, the Heart Protection Study,[8] to which large numbers of women and elderly individuals were recruited, showed no effect of the drugs on cancer. That said, the PROSPER population differed in age from the other trials used in the meta-analyses, and cancer risk in all statin trials that recruit elderly individuals should be assessed. In view of the available evidence, the most likely explanation is that the higher incidence in cancer rates in PROSPER was a chance finding, which could in part have been driven by the recruitment of individuals with occult disease.

Discussion

To arrive at a conclusion it would be worth summarizing the findings of the studies already discussed. We already knew from the SPARCL[31] and several other trials that aggressive, targeted reduction of LDL-cholesterol by statin treatment in patients younger than 75 years decrease CHD events including death CHD. Even large randomized controlled clinical trials including WOSCOPS,[5] AFCAPS/TexCAPS[42] and Heart Protection Study[14] have demonstrated consistent mortality benefit across patients without CHD. But these studies included only young and early elderly group and are, therefore, not the true reflections of septo & octogenarians to draw conclusion. AFCAPS/Tex CAPS trial[42] enrolled patients

up to 73 years of age, and as such, the study does not provide conclusive evidence of benefit with lipid lowering agent for primary prevention of CHD in patients beyond this age.

In PROSPER study[32], primary end point was a composite a coronary death, nonfatal MI, fatal & nonfatal stroke all of which was reduced substantially with pravastatin therapy given for 3 years. But as the study subjects had a history of, or risk factors for vascular disease, conclusive remarks cannot be put forward that pravastatin could be given in elderly individuals with dislipidaemia to reduce the risk of primary coronary disease, although PROSPER[32] advocated the same treatment strategy for elderly individuals as is currently used in middle aged people. New cancer diagnoses were more frequent on pravastatin than on placebo which is also a cause of concern but as this finding is incorporated in a meta-analysis of all pravastatin and all statin trials excess risk for cancer is ruled out. Pravastatin had no significant effect on cognitive function or disability. LIPID trial[7] demonstrated a significant increase in cancer rates among elderly patients assigned to pravastatin therapy. Kjekshus[22] included a total of 5011 patients at least 60 years of age with NYHA class II, III, or IV ischemic, systolic heart failure and randomly assigned them to receive 10 mg of rosuvastatin or placebo per day. The study concludes that Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations. The drug did not cause safety problems. As the sampled population of these studies was not representative of study population, they lack generalization.

In ALLHAT-LLT[19], pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants (n = 10355) aged 55 years and above with well-controlled hypertension and moderately elevated LDL-C with at least 1 additional CHD risk. It is the only study available in our hand that provided data on primary prevention of coronary artery diseases in elderly population of reasonable size. Although, the study subjects were not true representative of what we call elderly (septo & octogenarians), we can accept these data to come to a conclusion.

As statins are not free of side-effects, the most serious of which is muscle toxicity, as evidenced by the withdrawal of cerivastatin because of the excess fatal rhabdomyolysis risk. Though the risk of rhabdomyolysis appears to be low with the existing statins and might not negate the potential value of preventing CVD in patients who qualify for drug therapy, there is need to reconsider its adverse effects particularly in the elderly population.

Conclusion and Implications

The study concludes that statin therapy in elderly people may not provide additional benefit in the prevention of primary cardiovascular diseases or death due to primary cardiovascular events. Though most of the studies ruled out excess risk of cancer or other noncardiovascular events, their probability cannot be entirely ignored. The risk of adverse events of stain therapy in most of the studies is based on study subjects ranging from 55 years onwards and on an average duration of follow up of no more than 5 years. Inclusion of cancer-prone subjects in the study (septo & octogenarians) and long-term follow up beyond 5 years may prove otherwise. One study provided data that addition of statin to the existing drug schedule for different ailments of elderly subjects did cause drug interaction. Large-scale, multicenter, randomized trial on truly representative population with long term follow up will provide authentic data to answer the question whether statin therapy in elderly people with dyslipidaemia can prevent primary heart diseases. Until we do not have the answer in hand, routine prescribing of stain to treat dyslipidaemia in elderly people is discouraged and is left in the hand of treating physicians who using existing data and weighing risk benefit of individual patients will decide whether they will prescribe statin.

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